BLOOD CONSULTATIVE COMMITTEE NEWSLETTER, MARCH 2015

INTRODUCTION

Your chance to make a difference

Welcome to the latest update from the MHRA Inspectorate and SABRE teams, in lieu of a formal Blood Consultative Committee (BCC) meeting. The purpose of the newsletter is to make members of the BCC aware of relevant regulatory updates and 'hot topic' items, as an interim measure whilst MHRA is reviewing the current BCC meeting format. The newsletter is not intended as a permanent replacement for a face-to-face meeting, however MHRA is keen to look at more effective methods of communication to achieve a cascade to grass roots level considering the relative merits of the available platforms.

I would like to encourage the BCC Members to use the time between now and the meeting later this year to identify potential changes to the format and increase the value of the BCC meeting to the wider Health Care field. The date of the next face-to-face meeting is **Tuesday 29th September 2015**, so be prepared to contribute to what I hope will be a productive discussion and agreement of proposals to improve the effectiveness of the BCC.

Mark Birse
Group Manager Inspectorate

CONTENT

The topics covered in this newsletter are:

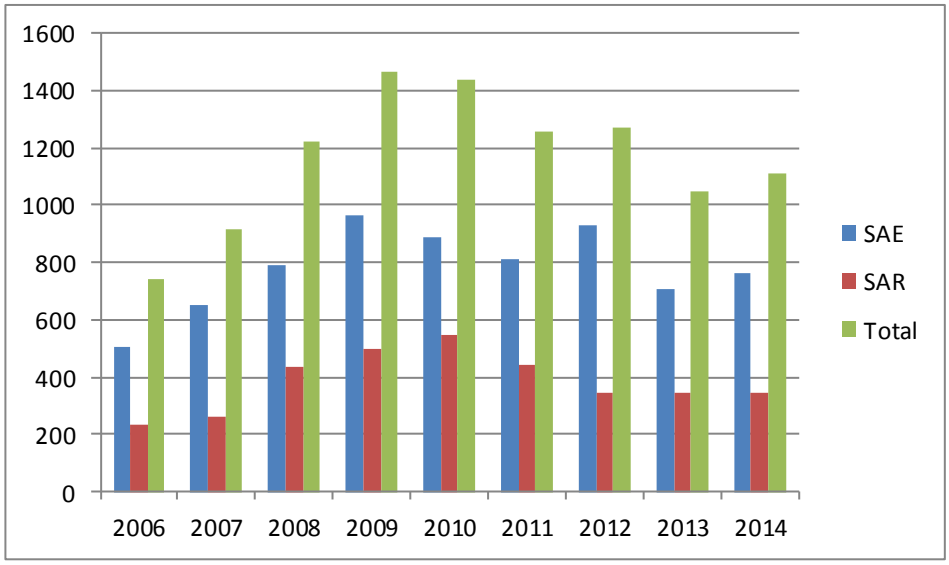
- SABRE update
- Regulatory update
- Inspectorate update
- Common inspection deficiencies at Blood sites
- Introduction to the Compliance Management Team (CMT)
- Feedback from GMDP Inspectorate stakeholder questionnaire 2014

SABRE UPDATE

The overall trends of reports have risen by approximately 8% from 2013, see table below.

	2013	2014
SAE	705	766
SAR	345	346
Total	1050	1116

The trend of SABRE reports, included in the summary by year, is highlighted in the figure below:



The number of SAEs reported shows an increase of 61 reports, 8% (705/766), from 2013 but still shows a significant drop, 21% (968/766), in reports received from its peak in 2009. The submitted SAR reports have stayed consistent with those SAR reports submitted in 2012 and 2013.

The following table shows the SAEs, by deviation and type, included in the annual report to Europe.

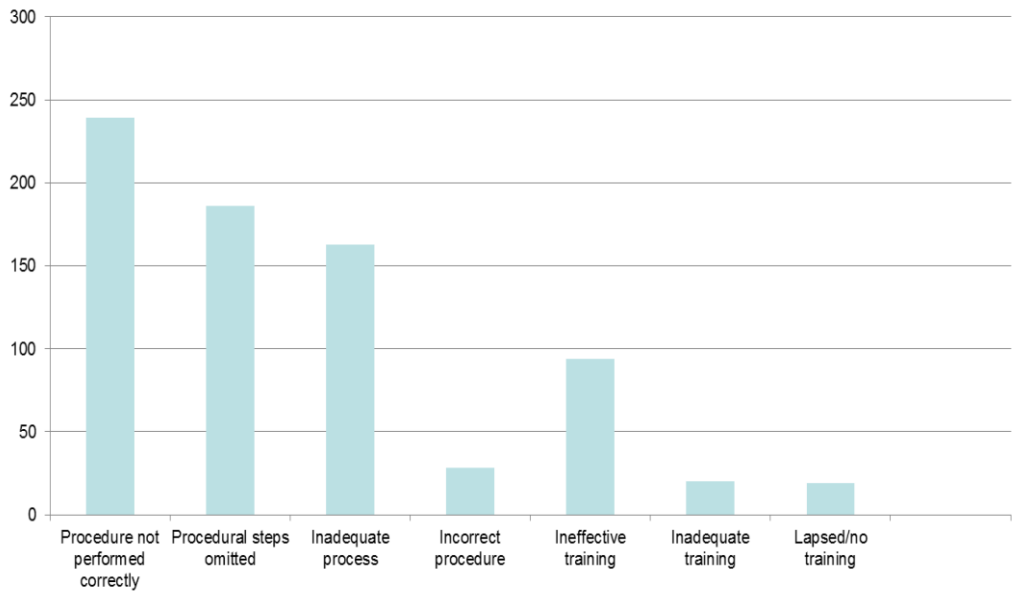
SAE Deviation	Total No	Product Defect	Equipment Failure	Human Error	Other
Whole Blood Collection	24	0	0	24	0
Apheresis Collection	5	4	0	1	0
Testing of Donations	11	0	1	9	1
Processing	11	0	0	11	0
Storage	212	0	6	206	0
Distribution	24	0	1	23	0
Materials	1	1	0	0	0
Other	478	0	3	475	0
Overall Total	766	5	11	749	1

Human error still accounts for 98% (749/766) of SAE reports received with storage accounting for 28% (212/766). In order to better understand these types of error, SABRE has produced further sub categories for both Storage and Human error report types and are summarised below:

Human error sub categories

1. Procedural steps not performed correctly – Failure to carry out a step (s) correctly
2. Procedural steps omitted – Missing a key step or not following the procedure
3. Inadequate process – Inadequate design of a process or fundamental QMS failure
4. Incorrect procedure – Process not properly described
5. Ineffective training – Training regime not understood by operator
6. Inadequate training – Training process not fit for purpose
7. Lapsed or no training – Carrying out a procedure without any formal training

A summary of human error reports received in 2014 is displayed below:



The above diagram illustrates that the majority of these types of error occurs when staff either fail to carry out procedural steps correctly and/or omit a step altogether. By looking at a selection of reports interruptions and distractions make up the majority or reasons why these procedural errors occur. It is therefore crucial that organisations identify the true root cause, what caused the distraction and/or interruption, so a suitable and robust CAPA can be introduced.

Storage error sub categories

The following table illustrates the number of storage errors, and their SABRE sub categories, received in 2014 and their comparison with the number of reports received in 2013.

Storage Sub Classification	2013	2014	Change
30 minute rule	9	13	+4
component expiry	56	77	+21
Failure to action alarm	18	14	-4
Incorrect storage of component	73	43	-30
Miscellaneous	0	4	+4
Return to stock error	13	15	+2
Sample expiry	18	18	0
Security	7	7	0
Storage temp deviation	17	21	+4
total	211	212	

Overall there is no real change in the overall numbers reported between the two years but the component expiry sub category has increased by 28%. Many laboratories rely on a morning check to remove expired components, but often this was carried out too late as clinical staff had already used the blood overnight. In general successful CAPA needs to be implemented that involves establishing a process to remove expired components earlier, either at midnight or the evening before the unit was due to expire.

The number of error reports that have been classified as incorrect storage of components has seen a fall from 2013 (73/43). In these incidents components have either been placed under the wrong storage conditions (e.g. platelets in a refrigerator) or in unmonitored storage equipment (e.g. a ward drug refrigerator).

Summary of Deviation category 'Other'

As Other error reports are the largest deviation, to better understand these types of errors the MHRA have produced Other error type sub categories which are highlighted in the table below:

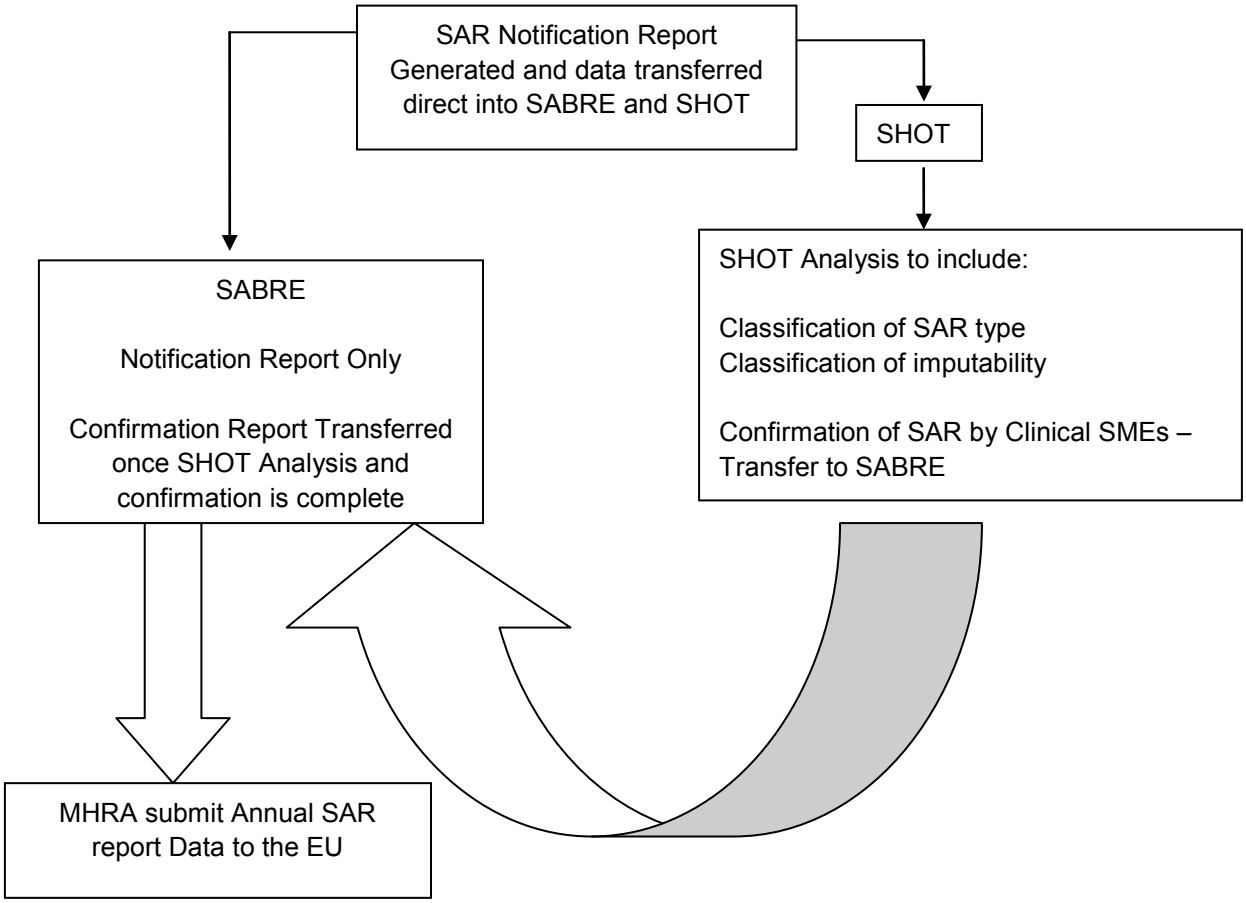
Sub Category	2012	2013	2014	Change from 2013
Incorrect Blood Component selected and issued (IBCI)	127	100	135	+35
Data Entry Error (DEE)	81	59	56	-3
Component Labelling Error (CLE)	75	82	85	+3
Sample Processing Error (SPE)	76	61	71	+10
Pre Transfusion Testing Error (PTTE)	64	53	68	+15
Component Available for Transfusion past de reservation Date (CATPD)	42	12	9	-3
Component Collection Error (CCE)	30	21	29	+8
Failed Recall (FR)	11	26	15	-11
Expired Component Available for Transfusion (ECAT)	7	10	4	-6
Incorrect Blood Component Ordered (IBCO)	5	3	5	+2
Incorrect Blood Component Accepted (From Supplier) (IBCA)	4	2	0	-2
Delayed Component Supply (BE Only) (DCS)	2	0	0	0
Unspecified (UNS)	4	1	1	0
Total	**528**	**430**	**478**	

Incorrect blood component issued (IBCI) errors remains the single largest 'other' sub category, comprising 28% (135/478) of the total reports received with special requirements not met being a common occurrence. Pre-transfusion testing errors (PTTE) comprised 14% (68/478) of the total 'other' errors reported. One notable area of improvement is the reduction of CATPD error reported, 43 to 9 (79%) since 2012. A full breakdown of these errors and a complete analysis has been done for the 2014 SHOT report.

Due to the differences in the SAR reporting processes of both SHOT and SABRE the figures published by both organisations are confusing to reporters and the EU therefore SAR reporting will see a fundamental change in 2015. In order to comply with the EU regulations the MHRA will receive all of the SAR notification reports in line with the BSQR regulation 'report as soon as known' but this information will be transferred to SHOT, from SABRE automatically, for a full investigation so the relevant clinical expertise can be utilised.

Once reports have completed the notification report in SABRE the data will be automatically transferred to the SHOT database. Reporters will only have to then complete the confirmation report, with the relevant investigation, in the SHOT database. Once the confirmation report is complete the relevant European data sets will be transferred back to SABRE, automatically, for reporting to the EU.

The proposed change is summarised as follows:



The differences in the two organisations reporting processes are highlighted in the 2014 figures below:

SARs reports, by imputability, reported to SABRE only in 2014

Total Confirmed reports 346

	IMPUTABILITY SCORE				
	NA	**0**	**1**	**2**	**3**
TOTAL SAR report by Imputability score	**3**	**61**	**108**	**127**	**47**

Total Confirmed 2014 SAR reports to SHOT and SABRE (TBC)

	SABRE	SHOT
SAR report received 2014	346	499

The table above shows the total number of SAR reports submitted to SABRE and SHOT.

The figures show that reporters have submitted 153 more SAR reports to SHOT than SABRE this highlights the fact that 30% (153/499) of SAR reports have been reported to SHOT only rather than reported to both organisations.

In previous years SAR data between the two organisations have differed and therefore caused some confusion for reporters. It is hoped that the new SAR reporting arrangements will avoid this confusion and produce more accurate SAR data.

REGULATORY UPDATE

Good Practice Guideline

The Council of Europe has completed drafting of the 18th edition of the Guide to the preparation, use and Quality Assurance of blood components. This will be issued in 2015. In April 2015 the Council of Europe GTS group will be meeting and it is envisioned that the drafting process for the 19th Edition will commence. The GTS group is comprised of Members from the wider EEA but also includes non EEA representatives from the US, New Zealand and Australia. Prior to the April meeting the inspectors blood interest group (a group comprising multiple European inspectors) will meet to discuss areas of update to the Good Manufacturing Practice (GMP) that may impact the good practice guide lines issued by EDQM.

The good practice guide is available at http://www.edqm.eu/site/good_practice_guidelines_dec_2013pdf-en-31298-2.html

This guide contains key elements of good practice that have been mainly derived from GMP guidelines but adapted for use with Blood and blood components. It is a 49 page document that has been extracted from the principles and standards of the Guide to preparation, use and Quality Assurance of blood components. The topic areas covered by the document are as follows:

Introduction

1. General principles – (includes Quality system management, general principles of good practice and Quality Risk Management)
2. Personnel and organisation - (Includes Training and key responsibilities)-
3. Premises – (Includes general principles of layout, Donor area, testing and processing areas and storage areas)
4. Equipment and Materials – (Includes: General requirements, Data processing systems, Qualification and validation)
5. Documentation - (Includes: General principles, types of document, document retention and Good Documentation Practices)
6. Blood collection, testing and processing – (Includes:Donor eligibility, collection, testing, processing and labelling)

7. Storage and distribution
8. Contract Management– (Includes: General principles, responsibilities, and contracts)
9. Non conformance – (Includes: Deviations, complaints Recall and CAPA)
10. Self inspection, audits and improvements
11. Quality monitoring and control

Note 1 ( ) highlight potential areas of interest, it does not cover the entire content of each section
Note 2: At present the good practice has not been ratified by the European Commission and therefore has no legal standing with regards to blood inspection, therefore for the immediate future, MHRA inspection will continue to cite findings against the Blood Safety and Quality Regulations (BSQRs) and relevant Directives in the first instance and against GMPS in the second instance.

INSPECTORATE UPDATE

Recruitment for the management positions within the realigned Inspectorate structure has been completed. The aim of the restructuring exercise was to bring the Inspectorate together as a cohesive team and better placed to sustain the highest possible level of public safety and improve the working environment for the team by identifying better ways of working and adopting best practice.

Andrew Gray has been appointed Unit Manager Inspection Operations with line management responsibility for GCP, GDP and GLP Inspection teams. Ian Jackson is the new Unit Manager Inspection Risk, Control & Governance. Andrew and Ian will work alongside Richard Andrews, Unit Manager Inspection Operations with line management responsibility for GMP and GPvP Inspection teams and Ian Rees, Unit Manager, Inspectorate Strategy and Innovation. Additionally Tracy Lovatt and Christine Gray have been appointed as GMDP Operation Managers and will work alongside Michelle Rowson with each having line management responsibility for one of the three teams of GMDP Inspectors.

Blood Compliance Report submissions April 2015

A change in approach to blood compliance report assessment during 2015 will see a removal of the majority of questions requiring free-text responses. There are no other significant changes to the BCR format proposed.

As a result of a reduction in the number of critical inspection deficiencies, compliance management and regulatory action cases, it is also proposed to reduce the number of inspections triggered ‘for cause’ as a direct result of the BCR assessment process. The inspectorate will develop the risk based inspection approach to react to risk factors identified throughout the year and maintain our commitment to proportionate regulation. Examples of non-BCR inspection triggers under consideration include notifications of significant site change and adverse SABRE reporting trends. Control inspections will also be performed to monitor the performance of the revised approach to BCR assessment and inspection scheduling.

Blood Facilities will not be required to complete a compliance report for 2015. An alternative system of compliance declaration will be implemented. This will be aligned with elements of the system implemented by the Health Products Regulatory Authority in Ireland.

COMMON INSPECTION DEFICIENCIES FROM BLOOD SITES

The following table shows the most common deficiencies observed at inspections of blood sites carried out by the GMDP Inspectorate in 2014.

Most Frequent Deficiencies Observed at Blood Sites		
Rank	**Defect Category**	**Percentage of Criticals / Major Deficiencies with this Defect Category**
1	**Investigation of anomalies – CAPA**	**13.7%**
=2	**Investigation of anomalies**	**6.5%**
=2	**Quality management – change control**	**6.5%**
4	**Personnel issues – training**	**5.0%**
5	**Personnel issues – duties of key personnel**	**4.3%**
=6	**Computerised systems – documentation and control**	**3.6%**
=6	**Quality management**	**3.6%**
=6	**Design and maintenance of premises**	**3.6%**
=6	**Equipment validation**	**3.6%**
=6	**Documentation - procedures/PSF/TAs**	**3.6%**
=6	**Design and maintenance of equipment**	**3.6%**
=6	**Warehousing and distribution activities (General Storage Temp Control and Monitoring)**	**3.6%**

To help put the deficiencies into context and to help sites better understand the issues identified, a more detailed review of the top 5 deficiencies is provided below:

Investigation of anomalies – CAPA (Corrective and Preventative Actions)
The main findings were:

- Sites did not have a CAPA handling procedures in place to enable tracking and trending and timely closure.
- Investigations into incidents lacked depth and scope, especially when looking at patient safety implications.
- Reports lacked detail of the root cause analysis and therefore the sequence of events

that led to the error. Without the appropriate investigation and identification of the root cause it is not possible to identify the appropriate CAPA.

- Timelines applied, within procedures, did not follow a risk based approach, neither identifying an appropriate timeframe, nor the level of investigation and the implementation of adequate control measures in line with the criticality of the incident.

- In some cases, that there was no formal process for the management and approval of extensions for investigations that were overdue according to the time limits detailed in organisations quality management systems.

Investigation of anomalies – Other findings

Investigation reports were weak and failed to create a comprehensive record for subsequent review. Examples of this are detailed below:

- The report failed to address how the issue was initially identified.

- The report assumed that no components were impacted but there was insufficient scientific rationale documented to support this assessment.

- No assessment was available of the operation of the equipment prior to the failure being reported.

- The report was written and approved by one member of Staff and lacked independent review.

The majority of the investigations that were reviewed had no clear outcome and with product disposition decisions poorly described. In addition there was no overarching procedure governing the investigations of incidents where several disparate processes were involved. The reports failed to describe and adequately link the error(s) to the quality system making the report difficult to follow and confusing for staff.

Another common finding was that there was an inappropriate use of risk management techniques in that the criticality scoring matrix was only based upon actual patient harm and failed to consider *potential* harm. In addition, the scoring matrix inappropriately classified incidents as ‘Medium risk’ when a severity of 5 (Death) and reoccurrence of 1 or 2 was recorded. In addition there was no assessment of how the incident was detected.

Quality management – Change control

Formal change control procedures continue to be problematic. Several examples were found where change control procedures were not been carried out correctly, as requests:

- Did not contain sufficient detail
- Not completed in an appropriate time frame

Change control procedures should be initiated with the appropriate amount of assessment and evidence. Examples have been found where a change control had been initiated when the decision to change a system/ process had already been made. In some cases changes had been made without any evidence of a change control process ever being followed.

Change controls documents were often seen that did not fully identify the prerequisites for the change to be implemented effectively and safely, it was therefore not clear how the final authorisation to make the new system live could be made in an informed manner.

Personnel issues – Training

Some organisations had weak training practices because of the following:

- Assessment of training against tasks and procedures was not formalised.
- Training records for on call personnel did not include training against critical procedures such as the recall process.
- Training of on call personnel was not kept up to date.
- Refresher training for ancillary personnel was not sufficiently frequent

Personnel issues – Duties of key personnel

Key duties must be assigned to appropriately trained and competent members of staff. The following deficiencies were found and include:

- Staff involved with root cause analysis had not had any formal root cause analysis training
- Audits of staff having the appropriate training for assigned tasks such as being authorised to access and remove blood from blood banks were visible.
- There was a lack of ownership of the quality management system by those outside of quality assurance.
- GMP training was not in place for all senior temporary appointments and also with staff that required it for their specific role.

INTRODUCTION TO THE COMPLIANCE MANAGEMENT TEAM (CMT)

The GMDP Inspectorate has implemented a non-statutory process to take action in response to poor compliance which does not yet meet the threshold for consideration of adverse regulatory action. The Compliance Escalation process forms an extension of the existing risk based inspection process, prior to consideration of regulatory action. The main aim of the process is to direct company towards a state of compliance, thus avoiding the need for regulatory action and the potential adverse impact to patient health through lack of availability of blood or medicines as a result of action against a hospital blood bank or blood establishment, as well as avoiding reputational damage for the site.

Compliance Escalation is managed via the Compliance Management Team (CMT); a non-statutory group of Senior GMDP Inspectors who coordinate and advise on compliance management activities arising from chronic or significant Good Practice deficiencies. The specific inspection case issues are considered by CMT, who make decisions in conjunction with the Inspector regarding the proportionate inspection and non-inspection compliance management actions required. This may include making recommendations on close monitoring of compliance improvement work through inspection, requested meetings with site senior management, and correspondence with the organisation's senior management, alerting them to the compliance concerns, and clearly outlining the consequences of continued non-compliance.

Decisions on compliance management actions are communicated to the organisation, following consideration of any written responses to a post inspection letter if relevant. The site Inspector(s) and CMT will continue to monitor the effectiveness of these actions. The CMT process may also be initiated by the Inspection Action Group (IAG) following referral for significant or serious GMP deficiencies. In cases where consideration of adverse regulatory action is no longer required due to improvements or mitigating actions, IAG may close their case referral and request that CMT maintain compliance management oversight until completion of the remediation plans. Upon satisfactory conclusion of the remediation work, the organisation will be returned to the routine risk based inspection (RBI) programme, however referral for consideration of regulatory action may still occur if the required improvements are not achieved in a timely manner.

GMDP INSPECTORATE STAKEHOLDER QUESTIONNAIRE 2014

In May 2014, the GMDP Inspectorate invited organisations to respond to a stakeholder feedback questionnaire. This is a process that has been in place for a number of years and has evolved from a paper based system to an on-line survey in order to encourage stakeholder participation. The questionnaire was extended in scope to cover inspect related activity, responding to queries and provision of technical information, and included free text fields to encourage stakeholders to provide details of their "could have been better" experiences.

Feedback was sought from organisations that had been inspected during the period of April 2013 – March 2014, and it was an opportunity for them to provide their views on the regulatory process. The responses received were representative of a range of stakeholders including manufacturers, wholesalers and NHS sites including the blood services.

95 stakeholders responded to the questionnaire and generally reported a very high level of satisfaction. Where opportunities for improvement were identified action plans have been developed. Specifically, Inspector workloads are being reviewed to ensure caseloads allow the Inspectors sufficient time to perform their full range of inspection related duties.

As the stakeholder feedback is anonymized by the IE&S Quality Manager, it is not possible to comment on any specific issues or concerns raised by Blood sites. However, by reviewing the free text responses, it is possible to attribute the following suggestions for improvement to NHS/Blood sites:

- Request to have more workshops as were originally provided following the BSQR. Seen as helpful to hospitals to have an informal atmosphere to discuss issues.
- Need for inspectors to have more experience of NHS establishments and understanding of the financial constraints that the NHS is under. Seen as helpful to hospitals that are not used to such a rigorous process.

The GMDP Inspectorate Management team recognise that improvements in the above areas can be achieved by effective communication and a pragmatic approach towards achieving regulatory compliance. Such improvement suggestions are consistent with the review of BCC communication methods to achieve a cascade to grass roots level.